REMARKS

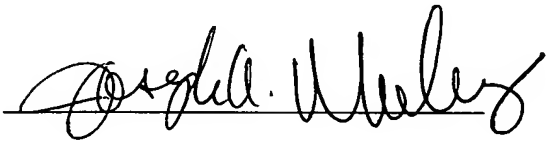
Applicants respectfully submit that no new matter has been added by the amendments to the claims or specification, or by the addition of new claims.

CONCLUSION

With entry of the above amendments and in view of the foregoing remarks, it is respectfully submitted that claims are in condition for allowance. Accordingly, allowance of the present claims is respectfully solicited. Applicants respectfully request early and favorable notification to that effect. Also submitted herewith, on a separate appended page titled "Version with Marking to Show Changes Made in the Specification and in the Claims," is a marked up copy of prior pending specification and claims.

The Examiner is urged to call the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

By: 

Joseph A, Mahoney
Reg. No. 38,956

Mayer, Brown, Rowe & Maw
P.O. Box 2828
Chicago, IL 60690-2828
(312) 701-8979
Dated: May 2, 2002

Version with Markings to Show Changes Made

In the Specification

1. The paragraph beginning on page 2, line 22 has been replaced with the following rewritten paragraph:

-- Testosterone circulates in the blood 98% bound to protein. In men, approximately 40% of the binding is to the high-affinity sex hormone binding globulin ("SHBG"). The remaining 60% is bound weakly to albumin. Thus, a number of measurements for testosterone are available from clinical laboratories. The term "free" testosterone as used herein refers to the fraction of testosterone in the blood that is not bound to protein. The term "total testosterone" or "testosterone" as used herein means the free testosterone plus protein-bound testosterone. The term "bioavailable testosterone" as used herein refers to the non-SHBG bound testosterone and includes [that] testosterone weakly bound to albumin.--

2. The paragraph beginning on page 8, line 16, has been replaced with the following rewritten paragraph:

-- Equally important, injection-based testosterone replacement treatments still create an undesirable pharmacokinetic profile. The profile generally shows a supra-physiologic testosterone concentration during the first 24 to 48 hours followed by a gradual fall – often to sub-physiologic levels – over [then] the next few weeks. These high serum testosterone levels, paralleled by increases in E_2, are also considered the reason for acne and gynecomastia occurring in some patients, and for polycythaemia, occasionally encountered especially in older patients using injectable testosterone esters. In the case of testosterone buciclate injections, the treatment barely provides normal androgen serum levels and the maximal increase of serum testosterone over baseline does not exceed 172 ng/dL (6 nmol/dL) on average. Because libido, potency, mood, and energy are thought to fluctuate with the serum testosterone level, testosterone

B

injections have largely been unsuccessful in influencing these variables. Thus, testosterone injection remains an undesirable testosterone replacement treatment method.—

3. The paragraph beginning on page 9, line 5, has been replaced with the following rewritten paragraph:

-- In the 1970s, researchers began using [with] oral, sublingual, or buccal preparations of androgens (such as fluoxymesterone, 17α-methyl-testosterone or testosterone undecanoate) as a means for testosterone replacement. More recently, researchers have experimented with the sublingual administration of testosterone-hydroxypropyl-beta-cyclodextrin inclusion complexes. Predictably, both fluoxymesterone and methyl testosterone are 17-alkylated and thus associated with liver toxicity. Because these substances must first pass through the liver, they also produce an unfavorable effect on serum lipid profile, increasing LDL and decreasing HDL, and carbohydrate metabolism. While testosterone undecanoate has preferential absorption through the intestinal lymphatics, it has not been approved in the United States.--

4. The paragraph beginning on page 9, line 14, has been replaced with the following rewritten paragraph:

-- The pharmacokinetic profiles for oral, sublingual, and buccal delivery mechanisms are also undesirable because patients are subjected to super-physiologic testosterone levels followed by a quick return to the baseline. For example, one recent testing of a buccal preparation showed that patients obtained a peak serum hormone levels within 30 minutes after administration, with a mean serum testosterone concentration of 2,688 +/- 147 ng/dL and a return to baseline in 4 to 6 hours. *See* Dobs et al., *Pharmacokinetic Characteristics, Efficacy and Safety of Buccal Testosterone in Hypogonadal Males: A Pilot Study*, 83 J. CLINICAL ENDOCRINOLOGY & METABOLISM 33-39 (1998). To date, the ability of these testosterone delivery mechanisms to

alter physiological parameters (such as muscle mass, muscle strength, bone resorption, urinary calcium excretion, or bone formation) is inconclusive. Likewise, researchers have postulated that super-physiologic testosterone levels may not have any extra beneficial impact on mood parameters such as anger, nervousness, and irritability.--

5. The paragraph beginning on page 10, line 13, has been replaced with the following rewritten paragraph:

-- FIG. 2 shows a typical pharmacokinetic [profile] testosterone profile for both the 40 cm^2 and 60 cm^2 patch. Studies have also shown that after two to four weeks of continuous daily use, the average plasma concentration of DHT and DHT/T increased four to five times above normal. The high serum DHT levels are presumably caused by the increased metabolism of 5α-reductase in the scrotal skin.--

6. The paragraph beginning on page 13, line 21, has been replaced with the following rewritten paragraph:

-- Researchers have recently begun investigating the application of DHT to the skin in a transdermal gel. However, the pharmacokinetics of a DHT-gel is markedly different from that of a testosterone gel. Application of [DTH-gel] DHT-gel results in decreased serum testosterone, E_2, LH, and FSH levels. Thus, DHT gels are not effective at increasing testosterone levels in hypogonadal men.--

7. The paragraph beginning on page 20, line 4, has been replaced with the following rewritten paragraph:

--FIG. 21(a) is a graph showing sexual motivation scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.—

B

8. The paragraph beginning on page 20, line 7, has been replaced with the following rewritten paragraph:

--FIG. 21(b) is a graph showing overall sexual desire scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

9. The paragraph beginning on page 20, line 10, has been replaced with the following rewritten paragraph:

--FIG. 21(c) is a graph showing sexual enjoyment (with a partner) scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

10. The paragraph beginning on page 20, line 13, has been replaced with the following rewritten paragraph:

--FIG. 22(a) is a graph showing sexual performance scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

11. The paragraph beginning on page 20, line 16, has been replaced with the following rewritten paragraph:

--FIG. 22(b) is a graph showing erection satisfaction performance scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

12. The paragraph beginning on page 20, line 19, has been replaced with the following rewritten paragraph:

--FIG. 22(c) is a graph showing percent erection scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

13. The paragraph beginning on page 21, line 1, has been replaced with the following rewritten paragraph:

--FIG. 23(a) is a graph showing positive mood scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

14. The paragraph beginning on page 21, line 4, has been replaced with the following rewritten paragraph:

--FIG. 23(b) is a graph showing negative mood scores on days 0 through 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

15. The paragraph beginning on page 21, line 7, has been replaced with the following rewritten paragraph:

--FIG. 24(a) is a bar graph showing the change in leg strength on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

16. The paragraph beginning on page 21, line 10, has been replaced with the following rewritten paragraph:

--FIG. 24(b) is a bar graph showing the change in arm strength on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

6

17. The paragraph beginning on page 21, line 13, has been replaced with the following rewritten paragraph:

--FIG. 25(a) is a bar graph showing the change in total body mass on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

18. The paragraph beginning on page 21, line 16, has been replaced with the following rewritten paragraph:

--FIG. 25(b) is a bar graph showing the change in lean body mass on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

19. The paragraph beginning on page 21, line 19, has been replaced with the following rewritten paragraph:

--FIG. 25(c) is a bar graph showing the change in fat mass on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

20. The paragraph beginning on page 22, line 1, has been replaced with the following rewritten paragraph:

--FIG. 25(d) is a bar graph showing the change in percent body fat on days 90 and 180 for hypogonadal men receiving either 5.0 g/day of AndroGel®, 7.5 g/day of Androgel®, 10.0 g/day of AndroGel®, or the testosterone patch.--

21. The paragraph beginning on page 24, line 7, has been replaced with the following rewritten paragraph:

-- A "penetration enhancer" is an agent known to accelerate the delivery of the drug through the skin. These agents also have been referred to as accelerants, adjuvants, and [sorption] absorption promoters, and are collectively referred to herein as "enhancers." This class of agents includes those with diverse mechanisms of action including those which have the function of improving the solubility and diffusibility of the drug, and those which improve percutaneous absorption by changing the ability of the stratum corneum to retain moisture, softening the skin, improving the skin's permeability, acting as penetration assistants or hair-follicle openers or changing the state of the skin such as the boundary layer.--

22. The paragraph beginning on page 26, line 18, has been replaced with the following rewritten paragraph:

-- Toxicity and therapeutic efficacy of the active ingredients can be determined by standard pharmaceutical procedures, *e.g.*, for determining LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic [induces] indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.—

23. The paragraph beginning on page 34, line 15, has been replaced with the following rewritten paragraph:

-- As shown in Table 8 and FIG. 5(a), at baseline, the average serum testosterone concentrations over 24 hours (C_{avg}) were similar in the groups and below the adult normal range. Moreover the variations of the serum concentration (based on maximum and minimum

concentrations during the 24-hour period, C_{max} and C_{min}, respectively) during the day were also similar in the three groups. FIG. 5(a) shows that the mean testosterone levels had a [the] maximum level between 8 to 10 a.m. (*i.e.*, at 0 to 2 hours) and the minimum 8 to 12 hours later, demonstrating a mild diurnal variation of serum testosterone. About one-third of the patients in each group had C_{avg} within the lower normal adult male range on day 0 (24/73 for the 5.0 g/day AndroGel® group, 26/78 for the 10.0 g/day AndroGel® group, and 25/76 for testosterone patch group). All except three of the subjects met the enrollment criterion of serum testosterone less than 300 ng/dL (10.4 nmol/L) on admission.--

24. The paragraph beginning on page 37, line 11, has been replaced with the following rewritten paragraph:

-- FIG. 5(e) shows the 24-hour pharmacokinetic profile for the treatment groups on day 180. In general, as Table 8(e) shows, the serum testosterone concentrations achieved and the pharmacokinetic parameters were similar to those on days 30 and 90 in those patients who continued on their initial randomized treatment groups. Table 8(f) shows that the patients titrated to the 7.5 g/day AndroGel® group were not homogeneous. The patients that were previously in the 10.0 g/day group tended to have higher serum testosterone levels than those previously receiving 5.0 g/day. On day 180, the C_{avg} in the patients in the 10.0 g/day group who converted to 7.5 g/day on day 90 was 744 ng/dL, which was 1.7 fold higher than the[.] C_{avg} of 450 ng/dL in the patients titrated to 7.5 g/day from 5.0 g/day. Despite adjusting the dose up by 2.5 g/day in the 5.0 to 7.5 g/day group, the C_{avg} remained lower than those remaining in the 5.0 g/day group. In the 10.0 to 7.5 g/day group, the C_{avg} became similar to those achieved by patients remaining in the 10.0 g/day group without dose titration. These results suggest that many of the under-responders may actually be poorly compliant patients. For example, if a

B

patient does not apply AndroGel® properly (*e.g.*, preferentially from the placebo container or shortly before bathing), then increasing the dose will not provide any added benefit.--

25. The paragraph beginning on page 38, line 3, has been replaced with the following rewritten paragraph:

-- FIGS. 5(f)-(h) compare the pharmacokinetic profiles for the 5.0 g/day AndroGel® group, the 10.0 g/day AndroGel® [g/day] group, and the testosterone patch group at days 0, 1, 30, 90, and 180, respectively. In general, the mean serum testosterone levels in the testosterone patch group remained at the lower limit of the normal range throughout the treatment period. In contrast, the mean serum testosterone levels remained at about 490-570 ng/dL for the 5.0 g/day AndroGel® group and about 630-860 ng/dL AndroGel® for the 10.0 g/day group.--

26. The paragraph beginning on page 48, line 12, has been replaced with the following rewritten paragraph:

-- As shown in FIG. 11 and Table 11, the serum SHBG levels were similar and within the normal adult male range in the three treatment groups at baseline. None of the treatment groups showed major changes from [these] the baseline on any of the treatment visit days. After testosterone replacement, serum SHBG levels showed a small decrease in all three groups. The most marked change occurred in the 10.0 g/day AndroGel® group.--

27. The paragraph beginning on page 54, line 15, has been replaced with the following rewritten paragraph:

-- Patients receiving AndroGel® or the testosterone patch achieve "hormonal steady state" only after long-term treatment. Specifically, data involving FSH and LH show that these hormones do not achieve steady-state until many weeks after treatment. Because testosterone concentrations are negatively inhibited by FSH and [LG] LH, testosterone levels do not achieve

B

true steady state until these other hormones also achieve steady state. However, because these hormones regulate only endogenous testosterone (which is small to begin with in hypogonadal men) in an intact feedback mechanism (which may not be present depending on the cause of hypogonadism), the level of FSH and/or LH may have little effect on the actual testosterone levels achieved. The net result is that the patients do not achieve a "hormonal steady state" for testosterone even though the C_{avg}, C_{min}, and C_{max} for testosterone remains [relative] relatively constant after a few days of treatment.--

28. The paragraph beginning on page 59, line 3, has been replaced with the following rewritten paragraph:

-- FIG. 18 and Table 21 show [shat] that serum procollagen generally followed the same pattern as serum osteocalcin. At baseline the mean levels were similar and within the normal range in all treatment groups. With transdermal treatment, serum procollagen increased significantly in all subjects as a group without treatment group differences. The increase in procollagen was highest on day 30 and then plateaued until day 120. By day 180, the serum procollagen levels returned to baseline levels.--

29. The paragraph beginning on page 62, line 19, has been replaced with the following rewritten paragraph:

-- Similarly the sexual performance score improved significantly in all subjects as a [groups] group. The improvement in sexual performance from baseline values was not different between transdermal preparations.--

30. The paragraph beginning on page 65, line 9, has been replaced with the following rewritten paragraph:

-- Muscle strength was assessed on days 0, 90, and 180. The one-repetitive maximum ("1-RM") technique was used to measure muscle mass in bench press and seated leg press exercises. The muscle groups tested included those in the hips, legs, shoulders, arms, and chest. The 1-RM technique assesses the maximal force generating capacity of the muscles used to perform the test. After a 5-10 minute walking and stretching period, the test began with a weight [believe] believed likely to represent the patient's maximum strength. The test was repeated using increments of about 2-10 pounds until the patient was unable to lift additional weight with acceptable form Muscle strength was assessed in 167 out of the 227 patients. Four out of 16 centers did not participate in the muscle strength testing because of lack of the required equipment.--

31. The paragraph beginning on page 67, line 9, has been replaced with the following rewritten paragraph:

-- FIGS. 25(c) and (d) show that the TFT and the PFT decreased in all transdermal AndroGel® treatment groups. At 90 days of treatment, TFT was significantly reduced by [in] the 5.0 g/day and 10.0 g/day AndroGel® groups, but was not changed in the testosterone patch group. This decrease was maintained at day 180. Correspondingly, at [the] day 90 and 180, the decrease in PFT remained significantly lower in all AndroGel® treated groups but not significantly reduced in the testosterone patch group.--

32. The paragraph beginning on page 67, line 15, has been replaced with the following rewritten paragraph:

-- The increase in TLN and the decrease in TFT associated with testosterone replacement therapy showed significant correlations with the serum testosterone level attained by the testosterone patch and the different doses of AndroGel®. Testosterone gel administered at

10.0 g/day increased lean mass more than the testosterone patch and the 5.0 g/day AndroGel® groups. The changes were apparent on day 90 after treatment and were maintained or enhanced at day 180. Such changes in body composition was significant even though the subjects were withdrawn from prior testosterone therapy for six weeks. The decrease in TFT and PFT was also related to the serum testosterone achieved and were different across the treatment groups. The testosterone patch group did not show a decrease in PFT or TFT after 180 days of treatment. Treatment with AndroGel® ([50] 5.0 to 10.0 g/day) for 90 days reduced PFT and TFT. This decrease was maintained in the 5.0 and 7.5 g/day groups at 180 days but were further lowered with continued treatment with the higher dose of the AndroGel®.--

33. The paragraph beginning on page 69, line 8, has been replaced with the following rewritten paragraph:

-- Skin irritation assessments were performed at every clinic visit using the following scale: 0 = no erythema; 1 = minimal erythema; 2 = moderate erythema with sharply defined borders; 3 = intense erythema with edema; and 4 = intense erythema with edema and blistering/erosion.--

In the Claims

1. (Amended) A method of treating hypogonadism in a male subject in need thereof, comprising[: applying a hydroalcoholic gel containing testosterone to] administering a composition to a selected area of skin of the male subject in [an] a pharmacologically effective amount [effective] to treat the hypogonadism, wherein the composition comprises:

a) about 0.1 % to about 10 % testosterone;

b) about 30 % to about 98 % alcohol selected from the group consisting of ethanol, and isopropanol;

c) about 0.1 % to about 5 % isopropyl myristate;

d) about 1 % to about 5 % sodium hydroxide; and

e) about 0.1 % to about 5 % gelling agent; and

wherein the percentages are weight to weight of the composition, and the testosterone is absorbed into the bloodstream of the subject at a rate and duration that maintains a circulating serum concentration of the testosterone greater than about 400 ng testosterone per dl serum during a time period beginning about 2 hours after administration and ending about 24 hours after administration.

2. (Amended) The method of claim 1, wherein the composition is administered daily for [application is for a period of] at least 7 days.

3. (Amended) The method of claim 1, wherein the composition is administered daily for at least about [period is at least] 30 days.

4. (Amended) The method of claim 1, wherein the composition is administered daily for at least about [period is at least] 180 days.

B

5. (Amended) The method of claim 1, wherein the administration [application] of the composition [hydroalcoholic gel] exhibits dose proportionality.

27. (Amended) The method of claim 1 [Claim 52], wherein the testosterone comprises an enantiomer, a racemic mixture, a derivative, [or] a base or a salt thereof.

53. (Amended) The method of claim 1 [Claim 52], wherein the composition administered [gel] weighs about 1.0 gram [grams] to 10.0 grams.

54. (Amended) The method of claim 1 [Claim 52], wherein the composition administered [gel] weighs about 2.5 grams to about 7.5 grams.

55. (Amended) The method of claim 1 [Claim 52], wherein the composition administered [gel] weighs about 2.5 grams to about 5.0 grams.

57. (Amended) The method of claim 1 [Claim 52], wherein the composition comprises [testosterone is present in a concentration of] about 0.5% to about 5% testosterone [weight to weight of the hydroalcoholic gel].

58. (Amended) The method of claim 1 [Claim 52], wherein the composition comprises [testosterone is present in a concentration of] about 1% testosterone [weight to weight of the hydroalcoholic gel].

60. (Amended) The method of claim 1 [Claim 52], wherein the composition comprises [isopropyl myristate is present in a concentration of] about 0.25 % [0.1%] to about 2.5 % isopropyl myristate [5% weight to weight of the hydroalcoholic gel].

61. (Amended) The method of claim 1 [Claim 52], wherein the composition comprises [isopropyl myristate is present in a concentration of] about 0.5% isopropyl myristate [weight to weight of the hydroalcoholic gel].

62. (Amended) The method of claim 1 [Claim 52], wherein the [hydroalcoholic gel further comprising] gelling agent is polyacrylic acid.

63. (Amended) The method of Claim 62, wherein the composition comprises about 0.9 % polyacrylic acid [polyacrylic acid is present in a concentration of about 0.1% to about 5% weight to weight of the hydroalcoholic gel].

64. (Amended) The method of claim 1 [Claim 52], wherein the composition comprises [alcohol is] about 40% to about 90% alcohol [ethanol weight to weight of the hydroalcoholic gel].

79. (Amended) The method of claim 86 [Claim 78], wherein the packet [further] comprises a polyethylene liner between the composition and inner surface [and] of the packet [composition].